

Remarks

The claims have been amended to simplify prosecution and to respond to some of the objections raised by the Office. The claims as amended are fully supported by the present specification and by the applications for which priority is claimed and which have been incorporated herein by reference. Support for new claim 166 is found, for example, in Table 6 on page 33 of U.S. Serial No. 08/344,824 which was incorporated into the present application by reference. This same table appears on page 33 of U.S. Serial No. 08/278,634 filed 21 July 1994 and incorporated herein by reference. That table indicates that a motif which binds to the stated HLA molecules contains a proline at position 2 and a hydrophobic amino acid at the C-terminus. The preferred amino acids are set forth in the table itself. Support for the requirement that the motif represented by proline at position 2 and a hydrophobic amino acid at the C-terminus occurs in a sequence of 8-11 amino acids is found on page 3 of the specification, lines 19-21. Similar paragraphs occur in the parent and grandparent applications. Support for the concept that the ability to bind at least one HLA within this group provides the likelihood that the peptide will be immunogenic is found on page 5 of the present application, lines 13-15 and at similar locations in the parent and grandparent applications. (In the grandparent, it is on page 5, lines 1-3.) Support for additionally testing for the ability of the peptide to elicit a restricted specific cytotoxic T-cell response found at page 11 of the present application, beginning at line 33 and at same location in the parent and in the grandparent application on page 10, beginning at line 33. Thus, no new matter has been added and entry of the amendment is respectfully requested.

The Invention

The invention is directed to a method to identify and prepare peptides which will be immunogenic in a substantial segment of the population - *i.e.*, will elicit an immune response which is restricted by HLA molecules encoded by more than one allele. The present inventors have identified the cross-reactivity of a particular motif with respect to a multiplicity of such

alleles as described in the specification. No document appears to have been cited which even suggests this cross-reactivity.

Formal Objections

Requirements for a submission in compliance with 37 C.F.R. § 1.821-1.825 is noted. A submission in accordance with this requirement is mailed under separate cover.

Also noted is the requirement for an additional oath; a supplementary oath will follow.

The "New Matter" Rejection

It is believed that most of the items set forth in connection with this rejection have been addressed by the claims as amended. For completeness, however, applicants respond to the specific points raised as follows. The numbering follows that set forth in the Office action.

1. The objected-to terminology "epitope consisting of about 8-11 residues that comprises an HLA B7 supermotif" is no longer present in the claims. Presence of amino acid sequence bearing a specified motif which contains 8-11 amino acids as required by the present claims is supported on page 3, lines 19-21. The specifics of the motif are supported in Table 6 as noted above.

2. The present claims no longer contain the term "HLA B7 supermotif" or "HLA structural supermotif."

3. The phraseology noted by the Office also no longer appears. The Office points to page 4 of the application, lines 19-25, which set forth preferred embodiments wherein 9 or 10 amino acids are contained. However, the application clearly states, as noted above, that the motif may contain 8-11 amino acids and Table 6 identifies the characteristics of these motifs.

It is believed that the objections in paragraphs 4-10 are now moot in view of the amended claims.

The Rejections Under 35 U.S.C. § 112, Second Paragraph

Again the paragraph identification used by the Office is used. The objection in paragraph a is moot because "natural source" no longer appears in the claims.

Paragraph b is also moot, as there is no longer claimed "A method for using a peptide fragment."

The improper Markush format no longer appears in the claims (paragraph c)

Paragraph d is moot as the claims no longer require preparing a first or second complex.

The objections of paragraph e are also moot as "about 8-11 amino acid residues" no longer appears.

Priority

As set forth above, the presently proposed claims 166-168 and 171-173 are clearly supported in the parent and grandparent applications. The only claims for which priority must be limited to the parent application are claims 169-170 and 174-175 which introduce alternative antigens of interest. It is believed this is proper as the claims are directed to a method to make peptides where the inventive nature of the method lies in the identification of the peptide to be made. Once the peptide is identified, conventional methods are used for synthesis. Thus, the inventiveness of the method does not depend on the identity of the peptide itself.

Rejections Under 35 U.S.C. § 103

There are three such rejections made to various of the claims previously pending, all of which cite Zakut-Houri, *et al.*, Harlow, *et al.*, Harris, *et al.*, or Lamb, *et al.*, in the alternative as primary documents. These documents teach the amino acid sequence of the human tumor antigen p53. This is admitted prior art; the invention does not lie in electing the p53 antigen in particular; rather the invention lies in a generic technique to identify a fragment of this antigen which is likely to be immunogenic in a substantial portion of the population. Thus, the rationale for the rejection must rest on the secondary documents.

The first such rejection relies on the combination of the primary references with all of Hill, *et al.*, Huczko, *et al.*, and Sette, *et al.* As the secondary documents are cited together rather than in the alternative, it is understood that teachings of all are required to defeat patentability. Sette, *et al.*, is not citable with respect to claims 166-168 and 171-173, since these claims are entitled to the priority of 21 July 1994. This article was published in January 1995.

With respect to claims 169-170 and 174-175 it will be noted that Sette, *et al.*, is the work of the present inventors. The remaining individuals listed as authors did not contribute to the concept of the present invention. No presumption that such a contribution would have been made arises by virtue of co-authorship. *In re Katz*, 687 F2d 450, 215 USPQ 14 (CCPA 1982). Accordingly, Sette, *et al.*, is not citable under 35 U.S.C. § 102(a) and thus not properly made the basis for rejection herein. In addition, it is respectfully submitted that Sette in combination with the remaining cited documents does not render the claimed invention obvious. There is no suggestion in any of Hill, Huczko or Sette that the method would yield a peptide which would be likely to elicit an immune response in individuals possessing any of a number of different HLA alleles. At best, Hill and Huczko teach individual peptides which are associated with binding to a single HLA molecule.

The second of these rejections is made with respect to a combination of the primary documents and Sidney, *et al.* Sidney, *et al.*, is clearly not citable with respect to claims 166-168 and 171-173 as it is published subsequent to the filing dates of the parent and grandparent applications for which priority is proper. With respect to the remaining claims as noted above, Sidney, like Sette, is the work of the inventors herein.

The third of these rejections is based on the combination of the primary documents with Hill and Huczko. This basis has already been addressed. There is no suggestion in Hill or Huczko that one make a peptide which is likely to immunize a large proportion of the population by seeking the required motif. Accordingly, this basis for rejection may be withdrawn.

With respect to all rejections, the combination of Hill and Huczko even if properly made fails to suggest that cross-reactivity of subsequences with the same residues in the anchor

positions over at least three alleles. Thus, these claims are free of the rejections for this reason alone.

The claims have been amended to clarify the nature of the invention and in response to certain formal objections. None of the cited documents suggest the claimed method to identify and prepare a peptide which has the ability to immunize individuals having different HLA-encoding alleles. Accordingly, it is believed that the proposed claims, claims 166-175 are in a position for allowance and passage of these claims to issue is respectfully requested.

In the unlikely event that the transmittal letter is separated from this document and the Patent Office determines that an extension and/or other relief is required, applicants petition for any required relief including extensions of time and authorize the Assistant Commissioner to charge the cost of such petitions and/or other fees due in connection with the filing of this document to **Deposit Account No. 03-1952** referencing docket no. 399632802000. However, the Assistant Commissioner is not authorized to charge the cost of the issue fee to the Deposit Account.

Respectfully submitted,

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